REMARKS

Examination of claims 5 and 9-15 is reported in the present Office action. Claims 5 and 9-15 are rejected under 35 U.S.C. § 112, first paragraph. The rejection is addressed below.

Sequence Listing

Applicants have amended the specification to conform to the sequence listing as originally filed. No new matter has been added.

Support for the Amendments

Support for the amendments is found throughout the specification as originally filed. For example, support for the amendment of the paragraphs that begin at page 6, line 15; page 8, line 23; page 9, line 13; page 16, line 10; page 25, line 3; page 28, line 18; page 53, line 3; page 58, line 20; and page 67, line 5, which replaces the term "antisense RNA" or "antisense nucleic acid" with "antisense oligonucleotide", is found at page 25, lines 3 and 4; at page 25, line 20; and at page 54, lines 10-21. Support for the amendment of the paragraph that begins at page 6, line 15, which replaces the term "decreases" with "increases," is found, for example, at page 16, lines 14-15. Support for the paragraphs inserted at page 8, line 23, which include a definition of the term "oligonucleotide," is found at U.S. Pat. No. 5,576,208, which is incorporated by reference at page 9, lines 6

and 7. Support for the amendment of the paragraphs beginning at page 17, line 15, and page 17, line 18, is found in the Sequence Listing as originally filed.

Support for the amendment of claims 5 and 8, which replaces the term "nucleic acid" with "oligonucleotide," is found at page 25, lines 3 and 4; at page 25, line 20, and at page 54, lines 10-21. No new matter has been added.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 5 and 9-15 are rejected as lacking enablement.

While the Examiner acknowledges that applicants have enabled methods for inducing apoptosis in cells *in vitro* and *in vivo* with a phosphorothioate modified antisense oligonucleotide that is 19 nucleotides in length, the Examiner asserts that applicants have failed to enable the full scope of the claimed methods; specifically, the Examiner asserts that applicants have failed to enable methods of using a modified or unmodified antisense oligonucleotide of any length other than 19 nucleotides. While applicants respectfully disagree, applicants have amended the claims to recite a modified antisense oligonucleotide. As detailed below, applicants' specification clearly enables the skilled artisan to make and use a modified antisense oligonucleotide, regardless of length, in the methods of the invention.

In the specification as filed, applicants provide detailed methods that allow the skilled artisan to predictably practice the methods of the invention. For example,

applicants disclose methods for the identification of antisense oligonucleotides (page 54, lines 10-21); methods for the rapid screening of IAP antisense therapies in cell lines (page 25, lines 10-22, and page 55, lines 8-18); methods for optimizing antisense therapies (page 55, lines 3-7); and methods for the *in vivo* delivery of therapeutic antisense oligonucleotides, including viral (pages 26 and 27), non-viral (page 27, line 21, to page 28), and injection methods (page 27, lines 5-9). In addition, applicants provide methods to test the efficacy of identified antisense oligonucleotides in animal models (pages 55 and 56), either alone or in combination with traditional therapies. A skilled artisan provided with applicants disclosure of XIAP sequences and using no more than routine methods could practice the full scope of the invention as claimed.

The sufficiency of applicants disclosure is evidenced in the Declaration of Dr. Robert Korneluk, previously of record, showing that applicants have successfully reduced to practice the present invention using techniques known to those skilled in the art of antisense oligonucleotide technology at the time of filing. Specifically, applicants i) identified antisense oligonucleotides; ii) screened IAP antisense therapies in cell lines; iii) tested the efficacy of identified antisense oligonucleotides in animal models; and iv) tested the efficacy of antisense oligonucleotides in combination with traditional therapies.

In support of the enablement rejection, the Examiner cites Chirila et al., (Biomaterials 23:321-342, 2002, hereafter "Chirila"), Jen et al. (Stem Cells 18:307-319, 2000, hereafter "Jen"), and Stein (Pharmacology & Therapeutics 85:231-236, 2000,

hereafter "Stein"), references that purportedly provide evidence that the use of oligonucleotides *in vivo* is unpredictable. As acknowledged by the examiner, applicants have demonstrated that the *in vivo* use of XIAP antisense oligonucleotides works as predicted. The only remaining issue is whether the use of an oligonucleotide *other* than a 19-nucleotide phosphorothioate modified antisense XIAP oligonucleotide is unpredictable.

To address the Examiner's concerns on this point, applicants provide Exhibits A (Shankar et al., J. of Neurochem. 79:426-436, 2001, hereafter "Shankar"), B (Kallio et al. FASEB J. express article, 10.1096/fj.01-0280fj3, 2001, hereafter "Kallio"), and C (Fukuda et al. Blood 100:2463-2471, 2002, hereafter "Fukuda"), which describe the use of modified and unmodified antisense oligonucleotides of varying lengths to decrease the expression of an IAP, i.e., human survivin.

Shankar: 20-mer antisense oligonucleotide

Shankar describes the use of phosphorothioate modified antisense oligonucleotides, 20 nucleotides in length, to downregulate expression of human survivin expression and to induce apoptosis in neural tumor cells in culture. At page 427, left column, lines 3-7, Shankar states:

> We have determined that SAO [Survivin antisense oligonucleotides] down-regulated survivin protein resulting in caspase-independent cell death in a neuroblastoma cell line, while an oligodendroglioma cell line underwent caspase-dependent apoptotic cell death.

The sequences of these antisense oligonucleotides are provided in Table 1, at page 427.

Kallio: 18-mer antisense oligonucleotide

Kallio describes the use of phosphorothioate antisense oligonucleotides, 18 nucleotides in length, to downregulate human survivin expression in HeLa and PtK1 cells in culture. At page 5, first paragraph, Kallio states, "In the HeLa cells transfected with the 2'-O-methoxyethyl chimaeric oligonucleotide at 200 and 400 nM concentrations, the endogenous survivin protein was reduced significantly in a concentration dependent manner by ~ 30% to 80% after survivin antisense targeting ($P<0.05$; 200 nM survivin antisense, $P<0.01$; 400 nM survivin antisense), whereas the scrambled control oligonucleotide had no effect (Fig. 1A)." This downregulation demonstrated a role for survivin in the regulation of chromosome segregation and mitotic exit. At page 1, Abstract, Kallio states, "We demonstrate that HeLa and PtK1 cells transfected or microinjected with survivin anti-sense oligonucleotides produce significantly more polyploidy and micronucleated progeny cells . . ."

Fukuda: full length antisense oligonucleotide

Fukuda describes the use of a full-length antisense survivin expression construct to modulate survivin expression in CD34 cells. Fukuda describes the production of a full-length antisense expression construct at page 2464, left column, lines 6-9,

> Full-length human and mouse survivin cDNAs were cloned into the MIEG3 plasmid. The orientation and sequence of every construct were confirmed before transfection. A clone showing a reverse direction was used as an antisense construct.

Mouse marrow cells were transduced with an antisense-mouse survivin construct. With

respect to these experiments, Fukuda states: "[R]educed survivin was observed in cells transduced with an antisense-mouse survivin (Figure 4A insert)." This construct modulated cell cycle and proliferation in mouse hematopoietic progenitor cells. At page 2463, right column, abstract, Fukuda states, "An antisense survivin construct decreased total and S-phase CFU-GM [granulocyte macrophage-colony-forming units]."

In sum, as evidenced in Shankar, Kallio, and Fukuda, an IAP antisense oligonucleotide, regardless of length or modification, works as predicted to decrease expression of an IAP target gene.

Antisense oligonucleotides in clinical use

In addition, applicants provide Exhibit D (Jansen et al., The Lancet Oncology 3:672-683, 2002; hereafter "Jansen"), which provides a review of the clinical use of modified antisense oligonucleotides varying in length from 18 to 26 nucleotides.

18-mer phosphorothioate antisense oligonucleotide

Jansen describes the *in vivo* use of an 18-mer phosphorothioate Bcl-2 antisense oligonucleotide during phase I/II trials (page 677, second paragraph). The 18-mer antisense oligonucleotide was administered in combination with dacarbazine to patients with advanced melanoma. With respect to these studies, Jansen states, "This trial also showed that G3139 causes down-regulation of BCL-2 protein in serial biopsy samples from patients with melanoma, and that this biological activity was associated with major

clinical responses (figure 5)."

20-mer mixed backbone antisense oligonucleotide

In addition, Jansen describes the *in vivo* use of an 20-mer mixed backbone DNA methyltransferase antisense oligonucleotide in early clinical testing (page 679, right column, second paragraph). The antisense oligonucleotide, MG-98, was administered to patients with advanced solid tumors. The antisense oligonucleotide successfully reduced levels of DNA methyltransferase mRNA, although no clinical benefit to the treated patients was observed.

20-mer phosphorothioate antisense oligonucleotide

Jansen also describes the use of a 20-mer phosphorothioate Protein Kinase C antisense oligonucleotide in a phase I/II clinical trial of a combination therapy for patients with non-small-cell lung cancer (page 678, left column, last paragraph). Patients who received the combination therapy showed a median survival of 18 months relative to a median 8 months survival time in patients receiving conventional therapy.

24-mer antisense oligonucleotide

Jansen describes a clinical pilot study that used a 24-mer phosphorothioate antisense oligonucleotide, LR-3001, to target the c-MYB proto-oncogene in bone-marrow cells harvested from patients with chronic myelogenous leukemia (page 679, right column, first paragraph). In this study, patients received chemotherapy with busulfan and cotoxan followed by re-infusion of mononuclear cells that were purged for 24 hours with

LR-3001. Four of 6 patients showed 85% to 100% normal metaphases 3 months after engraftment with the purged cells.

As evidenced in Jansen, antisense oligonucleotides, regardless of length or modification, work as predicted to silence their target genes. Applicants note that the references cited by the Examiner fail to provide specific technical reasons showing why varying the length or modification of an antisense XIAP oligonucleotide affects its ability to inhibit the biological activity of an IAP. To support a prima facie case of lack of enablement, specific technical reasons are always required (M.P.E.P. 2164.04). Thus, this basis for the enablement rejection should be withdrawn.

Inoperative embodiments

In further support of the enablement rejection, the Examiner asserts that applicants claimed invention encompasses antisense oligonucleotides that fail to downregulate XIAP expression. The Examiner states:

> . . . antisense oligonucleotides G3 and G4 are of the same length and are both complementary to XIAP mRNA, however G3 does not down regulate XIAP expression, and the G4 oligonucleotide does inhibit.

Contrary to the Examiner's suggestion, this example fails to show that applicants' claims are overly broad. The Federal Circuit has long held that it is not necessary for all possible embodiments of a claim to be operative in order for that claim to be enabled. *See Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ (Fed. Cir. 1984).

The proper test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1318 (Fed. Cir. 1985). In analyzing what constitutes undue experimentation, the MPEP (§ 2164.06) cites *In re Wands*, (858 F.2d 731, 8 USPQ2d 1400 (Fed Cir. 1988)):

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. (emphasis added)

The present situation is, in all important aspects, indistinguishable from the facts in *Wands* in which the Federal Circuit held that the applicant's claim was enabled, despite the necessity for screening a number of monoclonal antibodies, because the process of screening for antibodies that successfully bound antigen was straightforward. It follows that the present claims are also enabled, even if some screening would be necessary to identify the particular antisense oligonucleotides needed to induce apoptosis.

As detailed above, at the time of filing, a skilled artisan, using no more than routine experimentation and the teachings of the present specification, could easily screen XIAP antisense oligonucleotides to identify those that induce apoptosis in a mammalian cell *in vivo* or *in vitro*. Such screening could easily be accomplished using standard techniques for generating antisense oligonucleotides and thus does not constitute undue

experimentation. Thus, this basis for the enablement rejection should also be withdrawn.

In sum, applicants have clearly enabled the full scope of the pending claims. Accordingly, the enablement rejection should be withdrawn.

Return of Initialed Form PTO-1449 Requested

Applicants note that the Form PTO-1449, which was submitted with an Information Disclosure Statement filed on June 4, 2002, has not been initialed and returned in its entirety, and hereby request that page 3 of Form PTO-1449 be initialed and returned with the next Office action.

CONCLUSION

Applicants submit that this case is in condition for allowance, and such action is respectfully requested. If the Examiner does not concur, a telephonic interview with the undersigned is hereby requested.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 12/8/03

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